APOTEX CORP.

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August 23, 1999

Dockets Management Branch (HFA 305)
Food and Drug Administration
12420 Parklawn Dr. Rm. I-23
Rockville, MD 20857

RE: Comments Addressed to Docket Number 99D-0529, 99N-0193
Guidance for Industry
Changes to an Approved NDA or ANDA

To Whom It May Concern:

Apotex Corp applauds the efforts made to provide additional detail for post-approval changes. However, we have several comments and questions concerning the guideline. Our comments and discussions follow.

1. Line 105 – A. Validate the Effects of the Change

The term validate is used throughout this section. A definition listed in a footnote at the bottom of the page is provided that explains the differences between the use of this word here versus the cGMP definition of "validate". However, to many individuals, the cGMP definition is much more common, thus confusion still could result. We suggest the usage of the word assess or evaluate to better define the concept suggested.

2. Line 176

The section in which this line appears discusses the potential adverse effects of a change on the product. An example is presented in this sentence describing a change that could potentially result in a new degradent. References to qualification and identification of this degradent are made. We suggest adding definitions of these two concepts or references to the guideline that discusses these requirements in an in-depth fashion

3. Line 154 – Equivalence

This section discusses the assessment of a change and it's impact on identity, strength, quality, purity or potency. This is accomplished by comparing the new change to that previously approved. It is stated that this equivalence comparison may require a "criterion for comparison with calculation of confidence intervals relative to a predetermined equivalence interval." We suggest the addition of information as to what type of statistical evaluation and confidence intervals would be acceptable.

4. Line 217

In this paragraph there is discussion of evaluating a new facility as compared to that originally approved in the submission. Line 216 and 217 state that a prior approval supplement is required if the new facility differs materially from that previously approved. What is material to one individual may not be material to another. To add in the elimination of this inconsistency, we suggest further definition of "materially ". An additional statement to consult FDA or refer to the appropriate SUPAC document for further clarification of what "material" may mean in relation to the proposed change would be helpful.

5. Line 271

This section discusses the prior approval requirement for a "transfer of manufacturing of an aseptically processed sterile drug substance or sterile drug product to a newly constructed, refurbished or different aseptic processing facility." We suggest the addition of wording to reflect the location of the processing facility for which a prior approval supplement would be required. A move to a site on the same campus or to another room in the same facility, assuming processing, equipment and controls are equivalent, should not be considered a prior approval event. However, a move to a different campus would need to be evaluated much more closely and could fall under the prior approval requirements. Without this further detail, this section is ambiguous and could result in unnecessary filings.

6. Line 380

This sentence describes prior approval filing for "New equipment added to an aseptic processing line and made of different materials that come in contact with sterilized bulk solution or sterile drug components, or deletion of equipment from an aseptic processing line." Further clarification needs to be provided concerning the meaning of different materials. For example, are 304 and 316 stainless steel different?

7. Line 638

This sentence describes a prior approval-filing requirement for "changes in the size and/or shape of a container for a sterile drug substance or sterile drug product." However, it does not provide any criteria as to what is considered a change. Assuming the material of the container and all other packaging components remain the same and the previously validated depyrogenation/ sterilization parameters do not change, we suggest that this be an annually reportable event. If the change in container results in other criteria falling outside the validated parameters or the container is of a different material, we agree that this is a change that needs to be much more closely evaluated.

8. Line 795

This section describes the replacement of an in-house reference standard or reference panel (or panel member) as an annually reportable event. However, we suggest clarification as to whether this replacement implies the necessity of reporting the replacement of an old lot of reference standard with a new lot.

Apotex Corp. appreciates the opportunity to comment on this guideline.

Marcy Macdonald
KK

Marcy Macdonald
Associate Director
Regulatory Affairs

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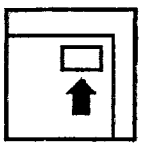

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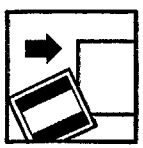

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